REMARKS

Claims 1 and 2 have been amended to specify that the compositions are a pharmaceutical composition comprising, in addition to the active agents, a pharmaceutically acceptable excipient. Support for this amendment is provided by page 5, line 22-23 and claim 9. Claims 10 and 14 have been amended to specify "inhibitor of the formation of nitric oxide" and now have antecedent basis provided by the claims from which they depend. Claims 9, 17 and 19 have been cancelled in view of the amendments to claims 1 and 2.

New claims 26 to 49 have been added. The claims are directed to more specific formulations and methods of treatments. Support for these claims is provided by the claims as originally filed and the description pages 2 to 5 which describes the various specific tubulin binding agent and nitrous oxide synthase inhibitors suitable for use in the present invention. In particular, support for

claims 26 and 45 is found at page 4 line 27;

claims 27 and 46 is found at page 4 lines 28 - 29;

claims 28 and 47 is found at page 4 lines 29 -30;

claims 29 and 41 is found at page 5 line 3;

claims 30 and 42 is found at page 5 line 12;

claims 31 and 48 is found at page 4 line 30, page 4 lines 28 - 29 and page 5 lines 4 - 12; and

claims 32 and 49 is found at page 4 line 30, page 4 lines 28 - 29 and page 5 lines 5 and 12.

Specific basis for the new method of treatment claim 33 is provided by page 2, lines 21 to 23 of the description.

Support for:

claim 34 is found at page 3 lines 5 - 6;

claim 35 is found at page 3 line 12;

claim 36 is found at page 4 lines 4 - 5.

claim 37 is found at page 4 lines 7 -8;

claim 38 is found at page 4 lines 9 - 10;

claim39 is found at page 4 line 11; and

claim 40 is found at page 4 lines 12 - 13.

Turning now to the specific issues raised in the official action, the Examiner has raised objections under 35 USC 112 to claims 4, 8, 17 and 19-21. The present claims address the objections raised and the Examiner is asked to reconsider these objections.

The spelling error on claim 4 has been corrected. The comment on claim 8, however, is not understood since this claim does not refer to "ortnithine".

The Examiner raised an objection to the antecedent basis for claims 10 and 14. The amendments to these claims addresses this objection. Claims 17, 19 and 20 have been canceled.

Turning now to the rejection under 35 USC 102 (b), the Examiner alleges claim 1 is anticipated by Bonfoco et al. The Examiner is respectfully requested to reconsider this rejection.

Present claim 1 is directed to a pharmaceutical composition for the treatment of a disease involving active angiogenesis which comprises a tubulin binding agent together with an inhibitor of the formation of nitric oxide in a mammalian system and a pharmaceutically acceptable excipient (emphasis added).

Bonfoco et al does not disclose a pharmaceutical composition according to the present invention. In Bonfoco et al, colchicine is used to damage the cytoskeleton in rat cerebellar cells to model neurological disorders such as Alzheimer's disease (Bonfoco p 189 col 2, last para. to page 190, col. para. 1). As part of the study the effect of various agents including NOS inhibitors such as NMMA or nitroarginine on the cell damage induced by colchicine exposure are studied.

The Examiner correctly indicates that Table 1 of Bonfoco describes an experiment in which cells are exposed to colchicine for 6 hours and then NMMA is added to the cells to observe the effect on NO_2- production. Bonfoco therefore only discloses colchicine and

NMMA together in the cell culture medium containing the rat cells. This is not a disclosure of a pharmaceutical composition according to claim 1 which requires, amongst other things, a pharmaceutically acceptable excipient.

The cell culture medium and rat cells in which the colchicine and NMMA are present in Bonfoco et al could in no way be described as a pharmaceutically acceptable excipient as required by the present claims. Therefore, the disclosure in Bonfoco is not a pharmaceutical composition according to the present claims.

It is therefore submitted that the invention as claimed in claim 1 is novel and meets the requirements of 35 USC 102.

Similarly, it is requested that the examiner reconsider and withdraw the rejection under 365 USC 103. The Examiner alleges that, Chaplin at al teaches that both vascular targeting agents and NO synthase inhibitors are used for the same purpose, which is incorrectly described to be "as anti-angiogenic agents". The Examiner then relies upon In re Kerkhoven to allege that it would be obvious to combine the two agents because they are both known to be useful for the same purpose.

However, the NO synthase inhibitors and vascular damaging agents described in Chaplin et al are not described therein as having the same purpose at all. It is clear from Chaplin et al that the mode of action of the NO synthase inhibitors and vascular targeting agents is not the same and as such the In re Kerkhoven analysis applied, by the Examiner is not appropriate. In Kerhoven, the issue before the court was the obviousness of a procedure in which two conventional spray dried detergents were mixed together. It was claimed that the resulting mixture would have good free-flow properties. The court concluded that " it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the veery same purpose." The court was not satisfied that there was sufficient evidence of superiority for the claimed product to overcome the prima facie case. However, this is not

the case in the present application. The purposes for which Chaplin discusses NO synthase inhibitors and vascular damaging agents are not the same.

Chaplin et al describes the effects of various agents on tumor blood flow and discusses how both the increase and decrease in tumor blood flow may be useful in treatment of tumors (see Chaplin, abstract). In Chaplin the effect of NO synthase inhibitors as vasoconstrictors are discussed (see page 153, col 2) as generally having the effect of reducing tumor blood flow. On the other hand the section on vascular damaging agents in Chaplin et al refers to a different mechanism altogether; namely the use of such agents to damage tumor blood vessels (see Chaplin page 157, col 2).

It is clear from Chaplin that whilst both agents may affect tumor blood flow the means by which this is achieved are very different and the Examiner has incorrectly over--generalized the Chaplin disclosure by describing both agents as "being useful for the inhibition of angiogenesis". In fact vascular damaging agents do not inhibit angiogenesis. Angiogenesis is the process by which new blood vessels are formed, for example in a tumor. On the other hand, vascular damaging agents (including the tubulin binding agents according to the present invention) act to damage newly formed vasculature (ie after the process of angiogenesis has already occurred). Thus the tubulin binding agents of the present invention are not anti-angiogenic agents, but work via a completely different mechanism by damaging newly formed vasculature which have formed as the result of inappropriate angiogenesis.

In view of the very different effects of the two agents used in the present invention, the In re Kerkhoven analysis applied by the Examiner is not appropriate because the two agents taught by Chaplin ore clearly not taught to be useful for the same purpose as required in the In re Kerkhloven case relied upon by the Examiner. Furthermore, there is nothing in the disclosure of Chaplin et al that would lead a skilled person to the presently claimed invention.

The present claims are not obvious over Chaplin et al. Chaplin et al provides a review of the effect of a large number of individual agents on tumor blood flow. In all cases the

agents are discussed and used in Caplin et al separately. The agents in Chaplin et al are very diverse in their nature and mode of action and include angiotensin II, hydralazine, nitric oxide inhibitors, nitric oxide scavengers, nitric oxide donors, endothelin receptor ligand, hyperoxic gases, nicotinamide and various vascular targeting agents. There is no suggestion in Chaplin et al of combining any of these many different agents together, let alone of making the specific combination of a nitric oxide inhibitor and a tubulin binding agent according to the present invention.

To arrive at the present invention starting from the disclosure of Chaplin et al a skilled person would have to take the following steps:

(i) to select a vascular targeting agent from the many agents in Chaplin et al;
(ii) to select a NO synthase inhibitor specifically from the many agents disclosed, and then;
(iii) to combine those specific agents together.

There is not even a remote suggestion in Chaplin et al of any of these steps, let alone all of them required to reach the present invention. It is submitted that a skilled person would only take such steps with the benefit of hindsight of the present invention. However, this luxury was not available to the skilled person at the time that the present invention was made. Bas~d upon the teaching of Chaplin et al there is nothing therein that would have motivated la skilled person to arrive at the present invention.

Furthermore, there nothing in Chaplin that would lead a skilled person to expect that the specific combination of a I, tubulin binding agent and an inhibitor of the production of nitrous oxide in accordance with the present invention would give an enhanced antitumour effect as observed lin the present invention.

As discussed above the presently claimed compositions and methods of treatment require the combination of a tubulin binding agent and an inhibitor of nitric oxide formation. It has been found that such a combination of agents provide a surprising antitumour effect

compared to !the administration of either agent alone.

The remarkable anti-tumor effects of the present invention is illustrated by the examples in the application. For instance, the Examiner is asked to consider Example 1 Table 1 which shows that treatment of SaS tumours using combretastatin A4 phosphate alone gave a tumor necrosis score of 1.7. The use of the nitrous oxide synthase inhibitor L-NAA alone gave a necrosis score of 2. On the other hand, the coadministration of combretastatin A4 and L-NAA gave a necrosis score of 9. Clearly the effect of the combination '!!is far greater than the use of either agent alone. Similar surprising anti-tumor effects are shown in Tables 2 and 3 showing the effects of the combinations according to the invention on tumor necrosis and vascular volume respectively. This could not have been predicted from the disclosure of Chaplin et al.

Given that Chaplin et al discloses only single agents and does not even remotely suggest that such agents) could be combined together, let alone that it would be advantageous to do so, It is submitted that the present claims represent a clear inventive step over Chaplin et al. The Examiner is therefore respectfully requested to withdraw this objection and' !allow the present application.

It is believed that this application should now be in order for allowance and an early action to this end is respectfully solicited.

Respectfully submitted,

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